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(54) Derivative of N-acetylcysteine having therapeutical activity, process for its preparation and related pharmaceutical compositions.

(57) The thioester of N-acetylcysteine with p-isobutylphenylpropionic acid simultaneously shows anti-inflammatory and mucolitic activities. It is prepared by reacting a reactive derivative of p-isobutylphenylpropionic acid and N-acetylcysteine at low temperature and in a polar solvent.

The salts with organic and inorganic bases, with basic aminoacids and with basic antibiotics having macromolecular structure, are stable and generally water soluble, whereby the active principle of the invention can be formulated for oral, parenteral, rectal and topical administration.

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EXAMPLE

A flask is charged with 600 mls of chloroform and 250 ml of SOCl_2 and this solution is slowly supplemented with 500 g of p-isobutylphenylpropionic acid. The latter is dissolved by lowering the temperature to a value near 0°C . Then a heating to $20-25^\circ\text{C}$ is carried out and at that point SO_2 and HCl are developed. The heating is slowly continued up to $60-63^\circ\text{C}$, the reaction being monitored on the basis of the gas development and until the latter ceases. The reaction mixture is concentrated under vacuum to eliminate the solvent and the unreacted thionyl chloride, and an oil is obtained which is used as such for the subsequent reaction. There are obtained 540 g of the chloride of the p-isobutylphenylpropionic acid

b) preparation of thioester of p-isobutylphenylpropionic of N-acetylcysteine

A flask is charged with 50 mls of water: after a cooling to a temperature of about 0°C , 16.32 g (0.1 moles) of N-acetyl-(L)-cysteine and 4 g of a 50% solution of NaOH are added. The reaction mixture is maintained under cooling at 0°C and there are slowly and simultaneously added 22.5 g of chloride of the p-isobutylphenylpropionic acid and 4 g of NaOH dissolved in 20 mls of water.

The reaction during this addition is exothermic and the temperature is controlled so that it is not higher than $+5^\circ\text{C}$. The reaction time is of between 3 and 5 hours. Upon the reaction is completed, the temperature is increased and then the volume is doubled with further water, the reaction mixture being then made acidic with HCl until a definitely acid pH is obtained.

The oily product is extracted with methylisobutylketone, the extract is dried over Na_2SO_4 , it is concentrated to dryness and a dense oil is obtained (yield: 32 g). The oil is dissolved in isopropyl alcohol, is filtered with carbon and concentrated again to dryness. A very dense oily product is obtained, which is chromatographically pure.

c) preparation of the salt of (DL)-lysine of p-isobutylphenylpropionylthio-N-acetylcysteine

These salts are readily obtained in solvents of the classes of ketones and alcohols by reacting one mole of erythromycin base or propionylerythromycin with one mole of p-isobutylphenylpropionylthio-N-acetylcysteine. The products are white, low melting crystals.

The products of the present invention show mucolithic activity, besides the anti-inflammatory activity, and can be used in all the possible pharmaceutical forms, such as tablets, capsules, syrups, suspensions, aerosols, normal or lyophilized vials, granulated formulations, creams, etc.

The thioester of N-acetyl-cysteine with p-isobutylphenylpropionic acid has been pharmacologically tested, with the following results:

1) Toxicity

It has not been possible to determine the LD_{50} since at the dose of 900 mg/kg no cases of death were revealed.

2) Anti-inflammatory activity The tests used for the evaluation of the anti-inflammatory activity were respectively that of the kaolin and that of the egg white.

a) Anti-inflammatory activity in the kaolin test. For each compound 16 rats of male sex, of the Sprague-Dawley strain and of 200-250 g of body weight, were used. The rats were divided into four groups each comprising four rats. All the animals were injected with a 10% suspension of kaolin. The first group was used as the control, whereas the other three groups were administered with doses respectively of 50, 75 and 100 mg/kg. The measurements of the diameters of the articulation were effected one hour after the kaolin injection and then every 24 hours.

The obtained data are reported in the table 1. The inoculation of kaolin caused an increase of the tibio-tarsal articulation which has been partially limited by the treatment with the test compound.

TABLE 1

Kaolin test

DOSES

Anti-inflammatory activity %

Controls

(Kaolin)

--

50 mg/kg

--

75 mg/kg

12

100 mg/kg

26

b) Egg white test.

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For each compound 16 male rats, of the Sprague-Dawley strain and weighing 300 g, were used. The animals were divided in four groups each comprising four rats. The first group served as a control, whereas the other three groups were orally administered, with a 30 minute interval, with two doses of 50, 75 and 100 mg/kg of the test compound.

The last administration was immediately followed by the inoculation of 0.1 ml of egg white in the rear paw of all the animals, including the controls.

The measurements of the diameters of the articulations were effected 3 and 4 hours later.

The data obtained in the present test are reported in the table 2.

TABLE 2

Egg white test

DOSES	Anti-inflammatory activity %
Controls	--
50 mg/kg	--
75 mg/kg	12
100 mg/kg	20

The thioester of N-acetylcysteine with p-isobutylphenylpropionic acid according to the present invention and the aforesaid salts are formulated by the known techniques, excipients, solvents, fillers, etc, giving place to pharmaceutical compositions in form of tablets, suppositories, injectable solutions, suspensions, syrups, emulsions, creams and aerosols.

In fact the stability and solubility of the subject compound and of its salts allow for such a complete range of uses.

CLAIMS

- 1) Thioester of N-acetylcysteine with p-isobutylphenylpropionic acid and the non toxic and pharmaceutically acceptable salts thereof with organic and inorganic bases.
- 2) Thioester according to claim 1, characterized in that said salts are formed with inorganic bases containing alkaline and earth-alkaline ions.
- 3) Thioester according to claim 1, characterized in that said salts are formed with basic aminoacids.
- 4) Thioester according to claim 3, characterized in that said basic aminoacids are arginine and lysine.
- 5) Thioester according to claim 1, characterized in that said salts are formed with basic antibiotics.
- 6) Thioester according to claim 5, characterized in that said basic antibiotics are erythromycin and propionylerythromycin.
- 7) A process for the preparation of the thioester of N-acetyl-cysteine with p-isobutylphenylpropionic acid, characterized in that a halide of the p-isobutylphenylpropionic acid is reacted with a derivative of N-acetylcysteine in a polar medium at an alkaline pH and at low temperature.
- 8) A process according to claim 7, characterized in that said halide is the chloride and said derivative of N-acetylcysteine is the sodium salt.
- 9) A process according to claim 7, characterized in that said polar medium comprises water or mixtures of water and dioxane and the reaction temperature is of between 0 and 5°C.
- 10) Pharmaceutical composition having anti-inflammatory and mucolithic activity, characterized by containing together with the common excipients and/or solvents, an effective amount of the thioester of N-acetyl-cysteine with p-isobutylphenylpropionic acid or a non toxic and pharmacologically acceptable salt thereof according to claims 1 to 6.
- 11) Pharmaceutical composition according to claim 9, in form of tablets, syrups and suspensions for the oral administration.
- 12) Pharmaceutical composition according to claim 9, in form of solution of the parenteral administration.

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13) Pharmaceutical composition according to claim 9, in form of suppositories for the rectal administration.

14) Pharmaceutical composition according to claim 9, in form of cream, ointment, aerosol and the like for topical administration.



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EUROPEAN SEARCH REPORT

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Application number

EP 81201309.2

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<p><u>EP - A1 - O 008 833</u> (OCE-ANDENO B.V.) (19-03-1980)</p> <p>* Page 10; claims 1,2 *</p> <p>--</p>	1	<p>C 07 C 153/07</p> <p>C 07 C 129/12</p> <p>C 07 C 101/24</p> <p>C 07 H 17/08</p> <p>A 61 K 31/265</p>
A	<p><u>US - A - 4 072 703</u> (JEAN BLUM)</p> <p>* Claims 1,2 *</p> <p>--</p>	1	
A	<p><u>US - A - 2 488 253</u> (E.H. WOODRUFF)</p> <p>* Column 2, lines 1-39; column 3, lines 21-29; claim 1 *</p> <p>--</p>	1,7,8,10	<p>TECHNICAL FIELDS SEARCHED (Int. Cl.)</p>
A	<p><u>CH - A - 274 379</u> (J.R. GEIGY AG)</p> <p>* Pages 1,2 *</p> <p>--</p>	1,7,8,10	<p>C 07 C 153/00</p> <p>C 07 C 149/00</p> <p>C 07 C 57/00</p>
A	<p>O.-A. NEUMÜLLER "Römpps Chemie Lexikon", 8th edition, vol. 1: A-CI, 1979</p> <p>FRANCKH'SCHE VERLAGSHANDLUNG, Stuttgart</p> <p>page 44</p> <p>--</p>	1,10	
A	<p>"ULLMANNS ENCYKLOPÄDIE DER TECHNISCHEN CHEMIE", 4th edition, vol. 7, 1974</p> <p>VERLAG CHEMIE, Weinheim/Bergstraße</p> <p>page 547</p> <p>----</p>	1,10	<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant</p> <p>A: technological background</p> <p>O: non-written disclosure</p> <p>P: intermediate document</p> <p>T: theory or principle underlying the invention</p> <p>E: conflicting application</p> <p>D: document cited in the application</p> <p>L: citation for other reasons</p>
X	The present search report has been drawn up for all claims		<p>&: member of the same patent family.</p> <p>corresponding document</p>
Place of search VIENNA		Date of completion of the search 12-02-1982	Examiner HERING